Amendments to the Specification:

Please replace the paragraph on page 3, beginning at line 19 with the following:

Alternative approaches to cancer imaging and therapy have involved the use of small molecules, such as peptides, that bind to tumor cell surface receptors. An In-111 labeled somatostatin receptor binding peptide, **In-111-DTPA-D-Phe^1-octreotide** ~~**In-111-DTPA-D-Phe^1-octeotide**~~, is in clinical use in many countries for imaging tumors that express the somatostatin receptor (Baker, *et al. Life Sci.,* 1991, 49, 1583-91 and Krenning, *et al., Eur. J. Nucl. Med.,* 1993, 20, 716-31). Higher doses of this radiopharmaceutical have been investigated for potential treatment of these types of cancer (Krenning, *et al., Digestion*, 1996, 57, 57-61). Several groups are investigating the use of Tc-99m labeled **analogs** ~~**ananlogs**~~ of **In-111-DTPA-D-Phe^1-octreotide** ~~**In-111-DTPA-D-Phe^1-octeotide**~~ for imaging and Re-186 labeled analogs for therapy (Flanagan, et al., U.S. 5,556,939, Lyle, *et al.,* U.S. 5,382,654, and Albert *et al.,* U.S. 5,650,134).

Please replace the paragraph on page 4, beginning at line 3 with the following:

Although improvements in cytotoxic chemotherapeutics have been made in recent years, the toxicity of these compounds to normal tissues has continued to severely limit their utility in extending survival in patients with solid tumors. Recently developed combinations of different therapeutic modalities, such as external beam irradiation and chemotherapy (*i.e.* chemoradiation), has provided some incremental benefit to the control of tumor progression and quality of life. However, neither systemic chemotherapeutics nor external beam irradiation have acceptable therapeutic indices, and are often limited due to unacceptable toxicity to normal tissues. The concept of combined therapy of cancer using anti-angiogenesis drugs in combination with chemotherapeutics is not new. Further, the concept of combining targeted in-vivo radiotherapy using radiolabeled antibodies and antibody fragments with chemotherapy has been reported (Stein R, Juweid M, Zhang C, *et al., Clin. Cancer Res.*, 5: 3199s-3206s, 1999). However, the combination of a angiogenesis-targeted therapeutic radiopharmaceutical which is targeted to receptors, which are then upregulated in

the neovasculature of tumors, together with chemotherapy has not been described before. Therefore, there is a need for a combination of a therapeutic radiopharmaceutical, which is targeted to localize in the neovasculature of tumors, with chemotherapeutics or a radiosensitizer agent, or a pharmaceutically acceptable salt thereof, to provide additive or synergistic therapeutic response without unacceptable additive toxicity in the treatment of solid tumors.

Please replace the paragraph on page 7, beginning at line 7 with the following:

Elevated levels of stromelysin (MMP-3) and interstitial collagenase (MMP-1) have been noted in synovial fluid derived from rheumatoid arthritis patients as compared to post-traumatic knee injury (Walakovits *et al.,* 1992, *Arth. Rheum.*, 35: 35) incorporated herein by reference.. Increased levels of mRNA expression for collagenase type I (MMP-1) and collagenase type IV (MMP-2) have been shown to be increased in ulcerative colitis as compared to Crohn's disease and controls (Matthes *et al.,* 1992, *Gastroenterology*, Abstract 661, incorporated herein by reference). Furthrmore, Anthony *et al.*, 1992, *Gastroenterology*, Abstract 591, demonstrated increased immuno-histochemical expression of the gelatinase antigen in **a rabbit** ~~**arabbit**~~ model of chronic inflammatory colitis.

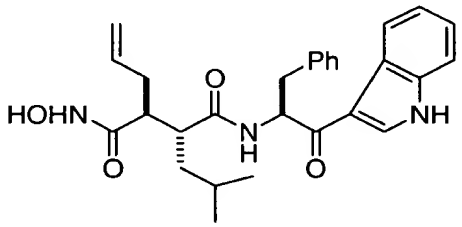
Please replace the paragraph on page 7, beginning at line 20 with the following:

It has been shown that the gelatinase MMPs are most intimately involved with the growth and spread of tumors. It is known that the level of expression of gelatinase is elevated in malignancies, and that gelatinase can degrade the basement membrane which leads to tumor metastasis. Angiogenesis, required for **the growth** ~~**thegrowth**~~ of solid tumors, has also recently been shown to have a gelatinase component to its pathology. Furthermore, there is evidence to suggest that gelatinase is involved in plaque rupture associated with atherosclerosis. Other conditions mediated by MMPs are restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound **healing, bone** ~~**healing,bone**~~ disease, proteinuria, aneurysmal aortic disease, degenerative

cartilage loss following traumatic joint injury, demyelinating diseases of the nervous **system,** **cirrhosis** ~~system,cirrhosis~~ of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, periodontal disease, age relatedmacular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neo-vascularization and corneal graft rejection. For recent reviews, see: (1) *Recent Advances in Matrix Metalloproteinase Inhibitor Research*, R. P. Beckett, A. H. Davidson, A. H. Drummond, P. Huxley and M. Whittaker, *Research Focus*, Vol. 1, 16-26,(1996), (2) *Curr. Opin. Ther. Patents* (1994) 4(1): 7-16, (3) *Curr. Medicinal Chem.* (1995) 2: 743-762, (4) Exp. Opin. Ther. Patents (1995) 5(2): 1087-110, (5) *Exp. Opin. Ther. Patents* (1995) 5(12): 1287-1196, all of which are incorporated herein by reference.

Please replace the paragraph on page 73, beginning at line 11 with the following:

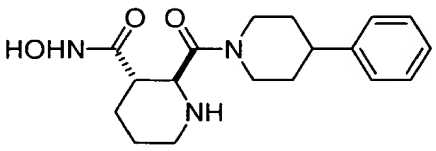
The P_3' position is a relatively open area in the succinyl hydroxamates, and a wide range of substitutents, see for example (7), may be introduced (Sheppard, G.S. et al, Bioorg. Med. Chem. Lett., 1998, 8, 3251) at this position. This position also offers the flexibility of attaching a variety of linkers and chelators for diagnostic purposes.



(7)

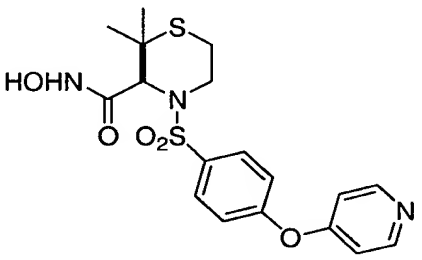
Other succinyl hydroxamates with modified P_2' and P_3' positions, such as (**8**) also have shown potent inhibition of MMP's. Those compounds and syntheses of them are further described in the following patent applications which are hereby incorporated by reference into this patent application: U.S. Patent Application Serial ~~Nos.~~ **No. 08/743,439 and U.S. Patent Nos.** ~~09/165,747~~ **US-A-6,057,336**, ~~08/743,439, 09/134,484~~ **US-B-6,576,664**,

~~09/247,675~~ US-B-6,455,522, ~~09/335,086~~ US-B-6,429,213, ~~09/312,066~~ US-B-6,365,587, ~~09/311,168~~ US-B-6,268,379, ~~60/127,594~~ US-B-6,495,548, and ~~60/127,635~~ US-B-6,376,665.

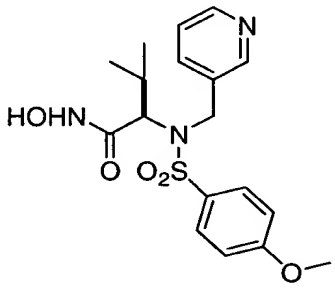


(8)

Another class of MMPIs is the sulfonamide hydroxamates, such as (**9**) and (**10**). Modification of the isopropyl substituent in (**10**) results in deep pocket MMP selectivity, for example MMP-2 vs MMP-1 (Santos, O. et al., J. Clin. Exp. Metastasis, **1997**,*15*, 499; MacPherson, L.J. et al, J. Med. Chem., **1997**, *40*, 2525).

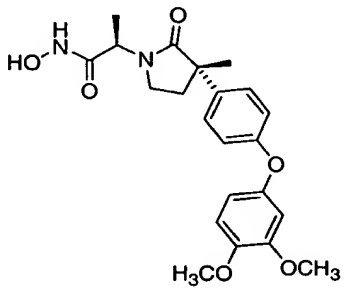


(9)

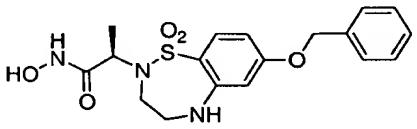


(10)

Selectivity for MMP-2 and MMP-9 was observed in the derivatized 'alanine' hydroxamates, such as compounds (**11**) and (**12**). The P_1 position is available for limited modification as described in the patents **and** applications incorporated by reference above.

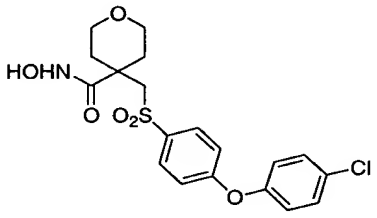


(11)



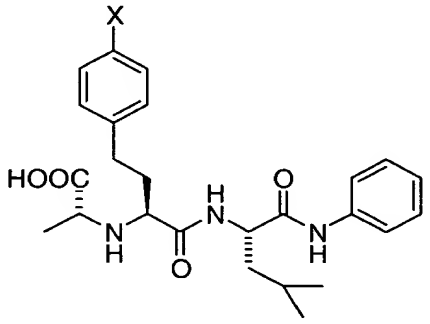
(12)

Other compounds with selectivity for MMP-2 and MMP-9 over MMP-1 include (**13**). In this example the alpha position has a quaternary carbon and the molecule does not contain any stereo centers (Lovejoy, B. et al., Nature Struct. Biol., **1999**, *6*, 217).



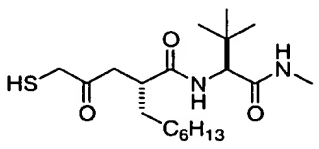
(13)

In the non-hydroxamate series a number of compounds have been reported with a variety of structures. Use of carboxylic acid as the ZBG has also received attention. In the case of compound (**14**), significant selectivity for MMP-2 (vs MMP-1) was observed when X = butyl vs X = H (Sahoo, S.P. et al, Bioorg. Med. Chem. Lett., **1995**, *5*, 2441).



(14)

Although thiols are monodentate ZBGs, some succinyl thiols such as (15) have exhibited good activity (Levin, J.I. et al, Bioorg. Med. Chem. Lett., 1998, 8, 1163). The P_3' position may be utilized to conjugate a variety of linkers and chelators (as described above) for the preparation of diagnostic agents.



(15)

Please replace the paragraph on page 77, beginning at line 15 with the following:

Multiple therapy comprises the use of the therapeutic radiopharmaceuticals of the present invention in combination with the compounds from the lists below which include chemotherapeutics, immunomodulators or colony-stimulating factors. The chemotherapeutic drugs include: Cytotoxics: mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, and lisuride. The steroids include: oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane. The biologics include: interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, leutinizing hormone releasing factor~~.~~ ;

Please replace the paragraph on page 86, beginning at line 16 with the following:

A number of methods can be used to attach the peptides, polypeptides, peptidomimetics, and non-peptides, Q, to paramagnetic metal ion or heavy atom containing solid particles, X^2, by one of skill in the art of the surface modification of solid particles. In general, the targeting moiety Q or the combination $(Q)_dL_n$ is attached to a coupling group that react with a constituent of the surface of the solid particle. The coupling groups can be any of a number of silanes which react with surface hydroxyl groups on the solid particle surface, as described in co-pending U.S. Patent Application Serial No. 09/356,178**, now US-B-6,254,852**, and can also include polyphosphonates, polycarboxylates, polyphosphates or

mixtures thereof which couple with the surface of the solid particles, as described in U.S. Patent No. 5,520,904.

Please replace the paragraph on page 92, beginning at line 1 with the following:

The most preferred technetium radiopharmaceuticals of the present invention are comprised of a hydrazido or diazenido bonding unit and two types of ancillary designated A_{L1} and A_{L2}, or a diaminedithiol chelator. The second type of ancillary ligands A_{L2} are comprised of one or more soft donor atoms selected from the group: phosphine phosphorus, arsine arsenic, imine nitrogen (sp^2 hybridized), sulfur (sp^2 hybridized) and carbon (sp hybridized); atoms which have p-acid character. Ligands A_{L2} can be monodentate, bidentate or tridentate, the denticity is defined by the number of donor atoms in the ligand. One of the two donor atoms in a bidentate ligand and one of the three donor atoms in a tridentate ligand must be a soft donor atom. We have disclosed in co-pending U.S. Patent No. 5,744,122, U.S. Patent Application Serial No. 60/013360**, now US-B-5,879,659,** and U.S. Patent Application Serial No. 08/646,886, the disclosures of which are herein incorporated by reference in their entirety, that radiopharmaceuticals comprised of one or more ancillary or co-ligands A_{L2} are more stable compared to radiopharmaceuticals that are not comprised of one or more ancillary ligands, A_{L2}; that is, they have a minimal number of isomeric forms, the relative ratios of which do not change significantly with time, and that remain substantially intact upon dilution.